



Docket No.: PF-0527-1 DIV

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title: PROSTATE GROWTH-ASSOCIATED MEMBRANE PROTEINS

Serial No.: 09/397,558

Filing Date: September 16, 1999

Examiner: Harris, A.

Group Art Unit: 1642

Commissioner for Patents
Box AF
Washington, D.C. 20231

DECLARATION OF LARS MICHAEL FURNESS
UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside,
Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of
Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to
Incyte.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry)

from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte to work in the Pharmacogenomics group, looking at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed Director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001, I founded Nuomics Consulting, Ltd., in Exning, UK, where I am currently employed as Managing Director. Nuomics Consulting, Ltd. provides expert technical knowledge and advice to businesses in the areas of genomics, proteomics, pharmacogenomics, toxicogenomics, and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on September 16, 1999 in the names of Preeti Lal et al. and was assigned Serial No. 09/397,558 (hereinafter “the Lal ‘558 application”). Furthermore, I understand that this United States patent application was a divisional application of, and claimed priority to, United States patent application Serial No. 09/083,521, filed on May 22, 1998 (hereinafter “the Lal ‘521 application”), having the identical specification. My remarks herein will therefore be directed to the Lal ‘521 patent application, and May 22, 1998, as the relevant date of filing. In broad overview, the Lal ‘521 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Lal ‘558 application contains claims that are directed to isolated polypeptides having either of the sequences shown as SEQ ID NO:1 and SEQ ID NO:2 (hereinafter “the SEQ ID NO:1 and SEQ ID NO:2 polypeptides”), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Lal ‘558 application does not disclose a specific and substantial asserted utility or a well established utility for the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides. I further understand that whether or not a patent specification discloses a specific and substantial asserted utility or a well established utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time the patent application was filed. In addition, I understand that a specific and substantial asserted utility or a well established utility under the patent laws must be a “real-world” utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner’s position that the Lal ‘558 application and its parent, the Lal ‘521 application, do not disclose a specific and substantial “real-world” utility for the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Lal ‘521 application pertains on May

22, 1998, would have concluded that the Lal '521 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in their then available and disclosed forms. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

"Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Lal '521 patent application disclosed to a person skilled in the art at the time of its filing a number of specific and substantial real-world utilities for the claimed SEQ ID NO:1 and SEQ ID NO:2 polypeptides. More specifically, persons skilled in the art on May 22, 1998, would have understood the Lal '521 application to disclose the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides as research tools in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Lal '521 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the

May 22, 1998 filing date of the Lal '521 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S., Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1991 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphrey-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F); and

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in gene and protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Lal '521 application on May 22, 1998 would have understood that application to disclose the SEQ ID NO:1 and SEQ ID NO:2 polypeptides to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

9. Turning more specifically to the Lal '521 specification, the SEQ ID NO:1 and SEQ ID NO:2 polypeptides are shown at pages 51-53 as two of seven sequences under the heading "Sequence Listing." The Lal '521 specification specifically teaches that the "invention features substantially purified polypeptides, prostate growth-associated membrane proteins, referred to collectively as 'PGAMP' and individually as 'PGAMP-1' and 'PGAMP-2.' In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, a fragment of SEQ ID NO:1, and a fragment of SEQ ID NO:2." (Lal '521 application at page 3, lines 5-9, as amended). With respect to SEQ ID NO:1, the Lal '521 specification teaches that (a) the identity of the SEQ ID NO:1 polypeptide was determined from a "prostate cDNA library", (b) the SEQ ID NO:1 polypeptide is the human prostate growth-associated membrane protein referred to as "PGAMP-1" and is encoded by SEQ ID NO:3, and (c) northern analysis shows that PGAMP-1 is expressed "in various libraries, at least 72% of which are immortalized or cancerous and at least 18% of which involve immune response. Of particular note is the expression of PGAMP-1 in cancerous or hyperplastic prostate (48%) and breast (7%)" tissues and therefore PGAMP-1 "appears to play a role in neoplastic and reproductive disorders" (Lal '521 application at page 13, lines 27-32; page 14, lines 10-13; and page 25, lines 15-17). With respect to SEQ ID NO:2, the Lal '521 specification teaches that (a) the identity of the SEQ ID NO:2 polypeptide was determined from a "breast cDNA library", (b) the SEQ ID NO:2 polypeptide is the human prostate growth-associated membrane protein referred to as "PGAMP-2" and is encoded by

SEQ ID NO:4, and (c) northern analysis shows that PGAMP-2 is expressed “in various libraries, at least 76% of which are immortalized or cancerous and at least 18% of which involve immune response. Of particular note is the expression of PGAMP-2 in cancerous or hyperplastic prostate (28%) and breast (10%)” tissues and therefore PGAMP-2 “appears to play a role in neoplastic and reproductive disorders” (Lal ‘521 application at page 14, lines 14-19; page 15, lines 4-8; and page 25, lines 20-22).

The Lal ‘521 application discusses a number of uses of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in addition to their use in gene and protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Lal ‘521 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides. Consequently, my discussion in this Declaration concerning the Lal ‘521 application focuses on the portions of the application that relate to the use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in gene and protein expression monitoring applications.

10. The Lal ‘521 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:1 and SEQ ID NO:2 polypeptides, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used “for the detection and/or quantification of nucleic acid or protein” (Lal ‘521 application at page 23, lines 5-8).

The Lal ‘521 application also discloses that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides are useful in other protein expression detection technologies. The Lal ‘521 application states that “[I]mmunological methods for detecting and measuring the expression of PGAMP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)” (Lal ‘521 application at page 23, lines 9-12). Furthermore, the Lal ‘521 application discloses that “[a] variety of protocols for measuring PGAMP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered

or abnormal levels of PGAMP expression. Normal or standard values for PGAMP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to PGAMP under conditions suitable for complex formation” (Lal ‘521 application at page 34, lines 2-6).

In addition, at the time of filing the Lal ‘521 application, it was well known in the art that “gene” and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length, and how that standard curve can be used in protein expression analysis (Tab A at p. 911). The Anderson 1991 article teaches that “there is a long-term need for a comprehensive database of liver proteins” (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the May 22, 1998 filing date of the Lal ‘521 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Lal ‘521 application, the Wilkins article, and other related pre-May 1998 publications, persons skilled in the art on May 22, 1998 clearly would have understood the Lal ‘521 application to disclose the SEQ ID NO:1 and SEQ ID NO:2 polypeptides to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in May 1998 (and for many years prior to May 1998) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are

specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identifying undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1987, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Lal '521 application, in particular regarding use of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies, and persons skilled in the art who read the Lal '521 application on May 22, 1998 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), in the mid-1980s the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the May 22, 1998 filing date of the Lal '521 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information... -- among others, ... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Lal '521 application clearly discloses that expression of PGAMP-1 and/or PGAMP-2 is associated with immortalized cell lines, cancerous and

hyperplastic prostate and breast tissue, and with the immune response (Lal '521 application at page 14, lines 10-13; page 15, lines 4-8; and page 25, lines 15-16 and 20-21). The Bjellqvist article showed that a protein may be identified accurately by its positional coordinates, namely molecular mass and isoelectric point (See Tab F). The Lal '521 application clearly disclosed SEQ ID NO:1 and SEQ ID NO:2 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on May 22, 1998 who read the Lal '521 application, would understand that application to disclose the SEQ ID NO:1 and SEQ ID NO:2 polypeptides to be highly useful in analysis of differential expression of proteins. For example, the specification of the Lal '521 application would have led a person skilled in the art in May 1998, who was using protein expression monitoring in connection with developing new drugs for the treatment of a neoplastic or reproductive disorder to conclude that a 2-D PAGE map that used the substantially purified SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 and SEQ ID NO:2 polypeptide sequences would be a more useful tool than a 2-D PAGE map that did not utilize these protein sequences in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating neoplastic and reproductive disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Lal '521 specification in May 1998, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be highly useful tools for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for neoplastic and reproductive disorders by means of 2-D PAGE maps, as well as for other evaluations.

(a) The Lal '521 specification contains a number of teachings that would lead persons skilled in the art on May 22, 1998 to conclude that a 2-D PAGE map that utilized the substantially purified SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides would be a more useful tool for gene and protein expression monitoring applications relating to drugs for treating neoplastic and reproductive disorders than a 2-D PAGE map that did not use the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides. Among other things, the Lal '521 specification teaches that (i) the identity of the SEQ ID NO:1 polypeptide was determined from a prostate cDNA library, (ii) the SEQ ID NO:1 polypeptide is the prostate growth-associated membrane protein referred to as PGAMP-1, and (iii) PGAMP-1 is expressed in various libraries derived from immortalized and cancerous tissues, cancerous or hyperplastic prostate and breast tissues, and tissues involved in the immune response, and, therefore, PGAMP-1 expression is "associated with neoplastic and reproductive disorders" (Lal '521 application at page 13, lines 27-32; page 14, lines 10-13; and page 25, lines 15-17; see paragraph 9, *supra*). Furthermore, the Lal '521 specification teaches that (i) the identity of the SEQ ID NO:2 polypeptide was determined from a breast cDNA library, (ii) the SEQ ID NO:2 polypeptide is the prostate growth-associated membrane protein referred to as PGAMP-2, and (iii) PGAMP-2 is expressed in various libraries derived from immortalized and cancerous tissues, cancerous or hyperplastic prostate and breast tissues, and tissues involved in the immune response, and, therefore, PGAMP-2 expression is "associated with neoplastic and reproductive disorders" (Lal '521 application at page 14, lines 14-19; page 15, lines 4-8; and page 25, lines 20-22; see paragraph 9, *supra*). The substantially purified SEQ ID NO:1 and SEQ ID NO:2 polypeptides could, therefore, be used as controls to more accurately gauge the expression of PGAMP in a sample, and consequently more accurately gauge the effect of a toxicant on expression of the gene.

Moreover, the Lal '521 specification teaches that SEQ ID NO:1 and SEQ ID NO:2 share chemical and structural homology with known tumor-associated antigens. PGAMP-1 shares chemical and structural homology with rat heat-stable antigen CD4. These polypeptides share 21% identity and two potential transmembrane domains (Lal '521 application at page 14, lines 6-8; and Figure 1). In addition, PGAMP-1 has chemical similarity with CD44 antigen precursor (Lal '521 application at page 14, lines 1-5). PGAMP-2 shares chemical and structural homology with human prostate-specific antigen and a fragment of the mouse apoptosis-associated tyrosine kinase, sharing

18% and 17% identity, respectively (Lal '521 application at page 14, lines 29-33; and Figures 2A, 2B, and 2C). In addition, all three of these proteins share six potential transmembrane regions and a potential signal peptide, and PGAMP-2 and human prostate-specific antigen have similar isoelectric points (Lal '521 application at page 15, lines 1-2).

(b) Persons skilled in the art on May 22, 1998 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detract from my conclusion that persons skilled in the art on May 22, 1998, having read the Lal '521 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating neoplastic and reproductive disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides. Persons skilled in the art on May 22, 1998 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:1 and/or SEQ ID NO:2 polypeptides because a 2-D PAGE map that utilized these polypeptides (as compared to one that did not) would provide more useful results in the kind of gene and protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to May 22, 1998.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Lal '521 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:1 and SEQ ID NO:2 polypeptides.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Lal '521 disclosure regarding the uses of the SEQ ID NO:1 and SEQ ID NO:2 polypeptides for protein

expression monitoring applications is not limited to the use of these proteins in 2-D PAGE maps. For one thing, the Lal '521 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Lal '521 application at, e.g., page 23, lines 3 to 31; and page 34, lines 2-10).

In addition, the Lal '521 specification repeatedly teaches that the proteins described therein (including the SEQ ID NO:1 and SEQ ID NO:2 polypeptides) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

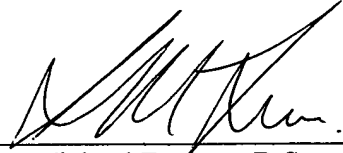
(a) Lal '521 application at p. 23, lines 9-12 ("Immunological methods for detecting and measuring the expression of PGAMP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)"); and

(b) Lal '521 application at p. 34, lines 2-10 ("A variety of protocols for measuring PGAMP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of PGAMP expression. Normal or standard values for PGAMP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to PGAMP under conditions suitable for complex formation[.] The amount of standard complex formation may be quantified by various methods, preferably by photometric means. Quantities of PGAMP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

Thus, a person skilled in the art on May 22, 1998, who read the Lal '521 specification, would have routinely and readily appreciated that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides, disclosed therein, would be useful to conduct gene and protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Lal '521 application. For example, a person skilled in the art in May 1998 would have routinely and readily appreciated that the SEQ ID NO:1 and SEQ ID NO:2 polypeptides would be useful tools in conducting protein expression analyses, using the 2-D PAGE mapping or western

analysis techniques, in furtherance of (a) the development of drugs for the treatment of neoplastic and reproductive disorders, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom
this 8th day of February, 2002.



**UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE**

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LIMITED RECOGNITION UNDER 37 CFR §10.9(b)

Terrence Lo is hereby given limited recognition under 37 CFR §10.9(b) as an employee of Incyte Pharmaceuticals, Inc. to prepare and prosecute patent applications wherein Incyte Pharmaceuticals, Inc. is the assignee of record of the entire interest in the application filed in the USPTO. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Terrence Lo ceases to lawfully reside in the United States; (ii) Terrence Lo's employment with Incyte Pharmaceuticals, Inc. ceases or is terminated; or (iii) Terrence Lo ceases to remain or reside in the United States on TN status.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: November 18, 2002


Harry I. Moatz
Director of Enrollment and Discipline